

Self-Study Modules on Tuberculosis

Treatment of Tuberculosis Infection and Disease

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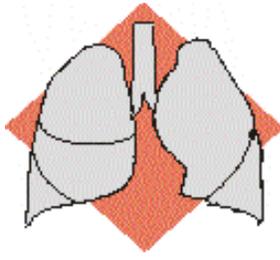
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Treatment of Tuberculosis Infection and Disease

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BACKGROUND

In this module, you will learn about the principles of treating TB infection and TB disease. TB infection is treated to prevent it from progressing to TB disease. This is called preventive therapy. Some TB-infected people are at very high risk of developing TB disease, and they should receive high priority for preventive therapy. TB disease is treated to cure the patient and to stop the spread of TB. As a public health worker, you may be responsible for helping TB patients take their medications as prescribed. This is very important, because patients with TB disease who do not complete treatment as prescribed may become infectious or develop drug-resistant TB.

This module also explains the possible side effects of the drugs used to treat TB infection and TB disease. If you have regular contact with TB patients, you should be aware of the signs and symptoms of these side effects. If a patient has symptoms of a serious side effect, you should notify a clinician immediately.

OBJECTIVES

After working through this module, you will be able to:

1. List the groups of people who should receive high priority for preventive therapy.
2. Explain the purpose of the medical evaluation for people who are being considered for preventive therapy.
3. Describe the usual preventive therapy regimen, the preventive therapy regimens for children and HIV-infected persons, and the preventive therapy regimen for people exposed to isoniazid-resistant TB.
4. Describe the possible adverse reactions to isoniazid.
5. Describe how patients should be monitored for adverse reactions to isoniazid.



Treatment of Tuberculosis Infection and Disease

6. Explain why TB disease must be treated for at least 6 months.
7. Describe the recommended regimen for the initial treatment of TB.
8. Describe the principles of preventing drug resistance.
9. Explain why directly observed therapy is important.
10. List the circumstances in which longer therapy may be necessary and the circumstances in which certain drugs should not be used for treatment.
11. List the common adverse reactions to the drugs used to treat TB.
12. Describe how patients should be monitored for adverse reactions to the drugs used to treat TB.
13. Describe how patients should be monitored for adherence to TB treatment.
14. Describe how patients should be evaluated for their response to treatment.
15. Describe the role of the public health worker in TB treatment.



NEW TERMS

Look for the following new terms in this module and in the glossary.

adherence to treatment – following the recommended course of treatment by taking all the prescribed medications for the entire length of time necessary

adverse reaction – negative side effect resulting from the use of a drug (for example, hepatitis, nausea, headache)

clinical evaluation – an evaluation done to find out whether a patient has symptoms of TB disease or is responding to treatment; also done to check for adverse reactions to TB medications

continuation phase – the period after the first 8 weeks of treatment, during which tubercle bacilli that remain after the initial phase are killed

daily regimen – a treatment schedule in which the patient takes a dose of each prescribed medication every day

directly observed therapy (DOT) – a strategy devised to help patients adhere to treatment; means that a health care worker or another designated person watches the TB patient swallow each dose of the prescribed drugs

ethambutol – a drug used to treat TB disease; may cause vision problems. Ethambutol should not be given to children who are too young to be monitored for changes in their vision.

hepatitis – damage to the liver, causing symptoms such as nausea, vomiting, abdominal pain, fatigue, and dark urine; hepatitis can be caused by several drugs used to treat TB infection or disease

initial phase – the first 8 weeks of treatment, during which most of the tubercle bacilli are killed

intermittent regimen – a treatment schedule in which the patient takes each prescribed medication two or three times weekly at the appropriate dosage

isoniazid – the drug that is most often used for preventive therapy and also used to treat TB disease; although relatively safe, it may cause hepatitis and other adverse reactions in some patients

liver function tests – tests done to detect damage to the liver



multidrug-resistant TB (MDR TB) – TB that is resistant to isoniazid and rifampin; more difficult to treat than drug-susceptible TB

peripheral neuropathy – damage to the sensory nerves of the hands and feet, causing a tingling sensation or a weakened sense of touch in the hands and feet

preventive therapy – medication that is given to people who have TB infection to prevent them from developing TB disease

pyrazinamide – a drug used to treat TB disease, usually during the initial phase of treatment; should not be given to pregnant women

relapse – the return of a disease after a partial recovery from the disease

rifampin – a drug used to treat TB disease; also used for preventive therapy in people with a positive skin test reaction who have been exposed to isoniazid-resistant TB. Rifampin has several possible side effects (for example, hepatitis, turning body fluids orange, drug interactions).

streptomycin – an injectable drug used to treat TB disease; may cause hearing problems. Streptomycin should not be given to pregnant women.



READING MATERIAL

Treatment of TB Infection (Preventive Therapy)

What is preventive therapy?

Preventive therapy is medication that is given to people who have TB infection to prevent them from developing TB disease.

Who should receive preventive therapy?

Some groups of people are at higher risk for TB than others (see Module 2, Epidemiology of TB). These groups are either

- # More likely to be exposed to or infected with *M. tuberculosis*, or
- # More likely to develop TB disease once infected

People in these groups should receive high priority for preventive therapy if they have a positive tuberculin skin test reaction (Table 4.1).

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People in certain groups should receive high priority for preventive therapy if they have a positive tuberculin skin test reaction.
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Table 4.1
High-Priority Candidates for Preventive Therapy

People in these groups should be given high priority for preventive therapy if they have a positive skin test reaction ¹ , regardless of their age:	People in the these groups should be given high priority for preventive therapy if they have a positive skin test reaction ¹ and they are younger than 35:
<ul style="list-style-type: none"># People with HIV infection²# Close contacts of people with infectious TB disease²# People whose skin test reaction converted from negative to positive within the past 2 years# People with chest x-ray findings suggestive of previous TB disease# People who inject illicit drugs# People with medical conditions that appear to increase the risk for TB disease (see Module 1, Transmission and Pathogenesis of Tuberculosis)	<ul style="list-style-type: none"># People born in areas of the world where TB is common (for example, Asia, Africa, or Latin America)# Low-income groups with poor access to health care# People who live in residential facilities (for example, nursing homes or correctional facilities)# Children younger than 4 years old# People in other groups as identified by local public health officials

¹ See Module 3, Diagnosis of Tuberculosis Infection and Disease, for information on classifying the tuberculin skin test reaction.

² In certain circumstances, people in these categories may be given preventive therapy even if they do not have a positive tuberculin skin test reaction.



People with no risk factors should be evaluated for preventive therapy if their tuberculin skin test reaction is ≥ 15 mm and they are younger than 35 years old.

People who may be exposed to TB on the job (for example, health care workers and staff of nursing homes or correctional facilities) should be evaluated for preventive therapy if they have a positive skin test reaction.

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Sometimes preventive therapy is given to people who have a negative tuberculin skin test reaction.
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Sometimes preventive therapy is given to people who have a negative tuberculin skin test reaction. For example, **some close contacts** may start taking preventive therapy if they have a negative skin test reaction but **less than 10 weeks** have passed since they were last exposed to TB. These contacts include

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Some close contacts may start taking preventive therapy if they have a negative skin test reaction but less than 10 weeks have passed since they were last exposed to TB.
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- # High-risk contacts who have a negative skin test reaction (including contacts who are **anergic**). High-risk contacts are young children, adolescents, HIV-infected people, and others who may develop TB very quickly after infection.
- # Close contacts who have a negative skin test reaction, if many other close contacts have a positive skin test reaction

Because less than 10 weeks have passed since they were last exposed to TB, these contacts may be infected with *M. tuberculosis* but have a false-negative skin test reaction (see Module 3, Diagnosis of Tuberculosis Infection and Disease). They should start preventive therapy to prevent them from rapidly developing TB disease. These contacts should be retested 10 weeks after they were last exposed to TB. If they have a negative skin test reaction, they can **stop taking preventive therapy**. (HIV-infected contacts may be



given a full course of preventive therapy, regardless of their skin test results.) If they have a positive skin test reaction, they should continue to take preventive therapy.

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Children younger than 6 months old who have been exposed to TB should start taking preventive therapy, even if they have a negative skin test reaction.
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Also, **children younger than 6 months old** who have been exposed to TB should start taking preventive therapy, even if they have a negative skin test reaction. This is because they are at high risk of rapidly developing TB disease and because they may have a false-negative reaction to the tuberculin skin test (see Module 3, Diagnosis of Tuberculosis Infection and Disease). The children should be retested when they are 6 months old. If they have a negative skin test reaction and 10 weeks have passed since they were last exposed to TB, the preventive therapy may be stopped.



Study Questions 4.1-4.4

- 4.1. What is the purpose of preventive therapy?**

- 4.2. Which groups of people should receive high priority for preventive therapy if they have a positive skin test reaction, regardless of their age? Name six.**

- 4.3. Which groups of people should receive high priority for preventive therapy if they have a positive skin test reaction and are younger than 35? Name five.**

- 4.4. In what circumstances may preventive therapy be given to people who have a negative tuberculin skin test reaction?**

Answers on pages 46-47.



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All persons being considered for preventive therapy should receive a medical evaluation.
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One reason for this evaluation is to exclude the possibility of TB disease.
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Another reason for the medical evaluation is to determine whether the patient has ever been treated for TB infection or disease.
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A third reason for the medical evaluation is to find out whether the patient has any medical problems that may complicate therapy or require more careful monitoring.
.....

Evaluation for Preventive Therapy

All people being considered for preventive therapy should receive a medical evaluation. One reason for this evaluation is to **exclude the possibility of TB disease**, because treating TB disease with a preventive therapy regimen (usually a single drug) can lead to drug resistance. To rule out the possibility of TB disease, clinicians should determine whether the patient has symptoms of TB disease, and they should evaluate the patient with a chest x-ray (see Module 3, Diagnosis of Tuberculosis Infection and Disease). People with symptoms of TB disease or chest x-ray findings suggestive of TB disease should be given treatment for TB disease, not TB infection.

Another reason for the medical evaluation is to **determine whether the patient has ever been treated for TB infection or disease**. People who have been adequately treated should not be treated again. The tuberculin skin test cannot be used to determine whether a patient has received treatment for TB infection or disease. This is because most people who have a positive skin test reaction will have a positive reaction if they are skin tested later in their lives, regardless of whether they have received treatment (see Module 3, Diagnosis of Tuberculosis Infection and Disease).

A third reason for the medical evaluation is to **find out whether the patient has any medical problems** that may complicate therapy or require more careful monitoring (for example, liver disease or alcoholism).



Case Study 4.1

You are sent to visit the home of a TB patient who was admitted to the hospital last week and diagnosed with infectious TB disease. Living in the home are his wife and his 1-year-old daughter. Neither one has symptoms of TB disease. You give them both a tuberculin skin test and return 2 days later to read the results. You find that the wife has 14 mm of induration, but the daughter has no induration.

Should either one start preventive therapy?

Why or why not?

Answers on page 53.



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The usual regimen for preventive therapy is isoniazid given daily for 6 months.
.....

Regimens for Preventive Therapy

The usual regimen for preventive therapy is a drug called **isoniazid** given daily for 6 months. Six months of isoniazid preventive therapy is very effective in preventing the development of TB disease in people not infected with HIV. Because isoniazid preventive therapy is not always effective when it is given for less than 6 months, every effort must be made to ensure that patients receive preventive therapy for at least 6 months.

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Children should receive at least 9 months of isoniazid preventive therapy. HIV-infected people should receive 12 months of isoniazid preventive therapy.
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Some groups of people should receive isoniazid preventive therapy for longer than 6 months. For example, **children** should receive at least **9 months** of isoniazid preventive therapy. **HIV-infected people** should receive **12 months** of isoniazid preventive therapy. In addition, people with chest x-ray findings suggestive of silicosis or previous TB disease should receive a 12-month regimen of isoniazid preventive therapy or a 4-month regimen of isoniazid and another drug, **rifampin**.

.....
Pregnant women should not be given preventive therapy until after delivery, unless they have certain medical conditions.
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For most **pregnant women** with TB infection, preventive therapy should be delayed until after delivery, even though isoniazid has NOT been shown to have harmful effects on the fetus. However, pregnant women who have certain conditions should receive preventive therapy right away if they are found to have TB infection. These conditions include HIV infection, recent TB infection, and other conditions that appear to increase the risk for TB disease (see Module 1, Transmission and Pathogenesis of Tuberculosis). The preventive therapy regimen for pregnant women is the same as the usual preventive therapy regimen — isoniazid given daily for 6 months.



Alternative Regimens for Preventive Therapy

In some situations, drugs other than isoniazid may be used for preventive therapy. For example, preventive therapy with **rifampin** is recommended for people with a positive skin test reaction who have been **exposed to isoniazid-resistant TB**. Preventive therapy with rifampin should be given for 6 months in adults and 9 months in children.

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In some situations, drugs other than isoniazid may be used for preventive therapy.
.....

No preventive therapy regimens have been studied for persons **exposed to TB resistant to both isoniazid and rifampin**. Persons at high risk of developing TB disease (for example, HIV-infected people) who are likely to be infected with multidrug-resistant organisms may be given an alternative preventive therapy regimen. This regimen should consist of two drugs to which the infecting organism is known to be susceptible. Two suggested regimens are ethambutol and pyrazinamide or pyrazinamide and a quinolone. Clinicians who are not experienced in managing patients exposed to drug-resistant TB should seek consultation from medical experts.

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No preventive therapy regimens have been studied for persons exposed to TB resistant to both isoniazid and rifampin.
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Study Questions 4.5-4.8

- 4.5. Name three reasons why patients should receive a medical evaluation before starting preventive therapy.**
- 4.6. Why is it important to exclude the possibility of TB disease before giving a patient preventive therapy?**
- 4.7. What is the usual preventive therapy regimen? How is it different for children and HIV-infected people?**
- 4.8. What preventive therapy regimen is recommended for people with a positive skin test reaction who have been exposed to isoniazid-resistant TB?**

Answers on pages 47-48.



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The major risk of isoniazid is hepatitis, or damage to the liver.
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Adverse Reactions to Isoniazid

Sometimes medications cause **adverse reactions**, or negative side effects. Isoniazid may cause **hepatitis**, or damage to the liver. Hepatitis prevents the liver from functioning normally, causing symptoms such as

- # Nausea
- # Vomiting
- # Abdominal pain
- # Fatigue
- # Dark urine

Many things can cause hepatitis, including various viruses and medications.

.....
Some factors, such as older age and alcoholism, increase the risk that isoniazid will cause serious hepatitis.
.....

Isoniazid can cause hepatitis in anyone. In fact, as many as 20% of people treated with isoniazid have some abnormality of **liver function tests** (tests done to detect damage to the liver) during treatment with isoniazid. In most people, these test results return to normal even when isoniazid treatment is continued.

In some people, however, there is a greater risk that isoniazid will cause serious hepatitis. Age is one factor; older persons are at higher risk for hepatitis. This is why preventive therapy is not recommended for people 35 years and older, unless their risk of developing TB disease is very high. Alcoholism, previous or current liver disease, drug injection, and the use of certain medications are other factors. In addition, some evidence suggests that women, particularly black and Hispanic women, are at increased risk for fatal hepatitis associated with isoniazid. This risk may be even greater for women who have recently given birth. However, fatal hepatitis is very rare.



.....
Isoniazid can damage the sensory nerves of the hands and feet.
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Isoniazid can also damage the sensory nerves of the hands and feet. This is called **peripheral neuropathy**. The main symptom of peripheral neuropathy is a tingling sensation or a weakened sense of touch in the hands and feet. Some conditions, such as alcoholism, diabetes, and malnutrition, increase the risk for peripheral neuropathy. People with these conditions should be given vitamin B₆ if they are taking isoniazid. Vitamin B₆ is also recommended for pregnant women who are taking isoniazid.

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All persons taking preventive therapy should be educated about the symptoms caused by adverse reactions to isoniazid.
.....

Monitoring for Adverse Reactions

First, all patients taking preventive therapy should be **educated about the symptoms that are caused by adverse reactions to isoniazid**. These patients should be instructed to stop taking the medication and seek medical attention immediately if these symptoms occur. **Second, all persons receiving preventive therapy should be evaluated at least monthly during therapy for signs and symptoms of adverse reactions**. During each monthly evaluation, clinicians should ask patients whether they have nausea, abdominal pain, or any of the other symptoms that may be caused by adverse reactions. In addition, they should examine patients for signs of these adverse reactions.

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All persons receiving preventive therapy should be evaluated at least monthly during therapy for signs and symptoms of adverse reactions.
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People at greatest risk for hepatitis should have liver function tests before starting isoniazid preventive therapy and every month during therapy. This includes

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People at greatest risk for hepatitis should have liver function tests before starting isoniazid preventive therapy and every month during therapy.
.....

- # People 35 years of age and older
- # People with a history of liver disease
- # People who abuse alcohol
- # People who inject illicit drugs
- # People who are taking other medications that may increase the risk of hepatitis



In addition, more careful monitoring — and possibly more liver function tests — should be considered for black and Hispanic women because they may be at increased risk for isoniazid-associated hepatitis. For all patients, isoniazid should be stopped if the results of liver function tests are much higher than the upper limit of the normal range.

Study Questions 4.9-4.10

4.9. What adverse reactions may be caused by isoniazid? Name two, and define each.

4.10. What are the symptoms of hepatitis?

Answers on page 48.



Study Questions 4.11-4.12

- 4.11. How often should patients be evaluated for signs and symptoms of adverse reactions during preventive therapy?**
- 4.12. Who is at greatest risk for hepatitis? What special precautions should be taken for these patients?**

Answers on pages 48-49.

Case Study 4.2

A 65-year-old man is prescribed isoniazid preventive therapy because he is a close contact of a person with infectious TB and he has an induration of 20 mm to the tuberculin skin test. His baseline liver function tests are normal, but he drinks a six-pack of beer every day.

What kind of monitoring is necessary for this patient while he is taking isoniazid?

Answer on page 54.



Treatment of TB Disease

Treating TB disease benefits both the person who has TB and the community. It helps the patient because it prevents disability and death and restores health; it benefits the community because it prevents the further transmission of TB.

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TB disease must be treated for at least 6 months; in some cases, treatment lasts even longer.
.....

TB disease must be treated for **at least 6 months**; in some cases, treatment lasts even longer. Most of the tubercle bacilli are killed during the first 8 weeks of treatment (the **initial phase**). However, a few bacilli become dormant (inactive), and they can remain dormant for a long time. The drugs used to treat TB do not work as well against dormant bacilli as they do against bacilli that are growing (active). Therefore, treatment must be continued for several more months to kill these few remaining bacilli (the **continuation phase**). If treatment is not continued for a long enough time, some bacilli may survive and cause TB disease at a later time (**relapse**).

.....
In most areas of the country, the initial regimen for treating TB disease should include four drugs: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin.
.....

In most areas of the country, the initial regimen for treating TB disease should include four drugs (Figure 4.1):

- # Isoniazid (INH)
 - # Rifampin (RIF)
 - # Pyrazinamide (PZA)
- and either

Ethambutol (EMB) or streptomycin (SM)
When the drug susceptibility results are available, clinicians may change the regimen accordingly. In areas where less than 4% of cases are resistant to isoniazid (first drug susceptibility test only), three drugs (INH, RIF, and PZA) may be adequate for the initial regimen.

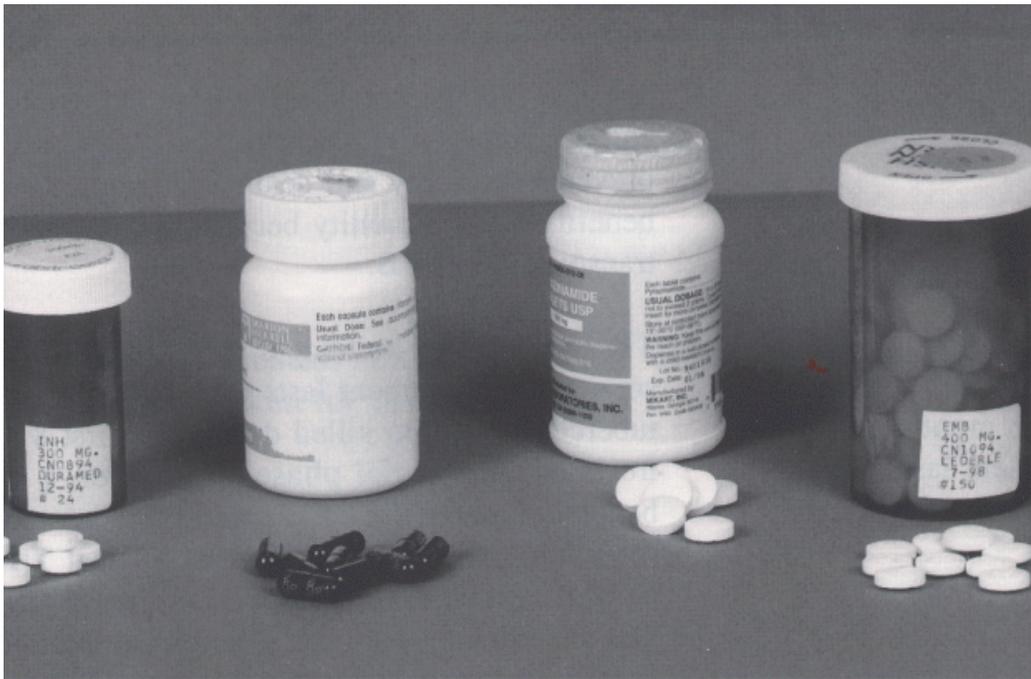


Figure 4.1 Drugs used to treat TB disease. From left to right: isoniazid, rifampin, pyrazinamide, and ethambutol. Streptomycin (not shown) is given by injection.



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TB disease must be treated with at least two drugs to which the bacilli are susceptible.
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Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment or when patients do not follow treatment regimens as prescribed.
.....

Preventing Drug Resistance

Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment. TB disease must be treated with **at least two drugs** to which the bacilli are susceptible. Using only one drug to treat TB disease can create a population of tubercle bacilli that is resistant to that drug. When two or more drugs are used together, each drug helps prevent the emergence of bacilli that are resistant to the other drugs. When a patient is not improving in response to a prescribed regimen, adding a single drug to that regimen may have the same effect as using only one drug for treatment: it can lead to drug resistance.

Drug resistance can also develop when patients do not follow treatment regimens as prescribed — in other words, if they do not take all of their pills, if they do not take their pills as often as prescribed, or both. When this happens, the patients may expose the bacilli to a single drug.



Study Questions 4.13-4.16

- 4.13. Why must TB disease be treated for at least 6 months?**
- 4.14. Which four drugs are recommended for the initial treatment of TB disease?**
- 4.15. Why should at least two drugs be used to treat TB disease?**
- 4.16. Name two factors that can lead to drug resistance.**

Answers on pages 49-50.



.....
In order to cure TB and prevent drug resistance, patients with TB must adhere to treatment.

Adherence to Treatment

Treatment for TB disease lasts longer and requires more drugs than treatment for other infectious diseases. In order to cure TB and prevent drug resistance, patients with TB must follow the recommended course of treatment. This is called **adhering to treatment**. However, ensuring that patients adhere to treatment can be difficult, because many patients are reluctant to take several different medications for many months.

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Directly observed therapy should be considered for all patients because there is no way to predict reliably which patients will adhere to treatment.

There are many ways to encourage patients to adhere to treatment. The most effective strategy is **directly observed therapy (DOT)**. DOT means that a health care worker or another designated person watches the TB patient swallow each dose of the prescribed drugs. This method of treatment should **be considered for all patients** because there is no way to predict reliably which patients will adhere to treatment. DOT should be done at a time and a place that are convenient for the patient. For example, health care workers can meet TB patients at work, at home, or in other locations to provide DOT.

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Another way to improve patient adherence is to offer incentives or enablers.

Another way to improve patient adherence is to offer **incentives** or **enablers**. Incentives are small rewards given to patients to encourage them to take their own medicines or to keep their DOT or clinic appointments. For example, patients may be given food, restaurant coupons, clothing, or other items as an incentive. Enablers are things that help the patient receive treatment, such as bus tokens to get to the clinic. Incentives and enablers should be chosen according to the patient's needs, and they are frequently offered along with DOT.



.....
An important part of helping
patients take their medicine
is to educate them about TB.
.....

An important part of helping patients take their medicine is to **educate them about TB**. This means talking to them about the cause of TB, the way TB is spread, the methods of diagnosing TB, and the specific treatment plan. Patients who understand these concepts are more likely to adhere to treatment.

In summary, in order to prevent relapse and drug resistance, clinicians must **prescribe an adequate regimen** and **make sure that patients adhere to treatment**.

Treatment Regimens

There are several options for daily and intermittent treatment. The recommended regimens are described in Table 4.2; the recommended dosages for the most common drugs are listed in Table 4.3. These tables are provided for you to use as a reference.

Table 4.2
6-Month Regimen Options¹ for Pulmonary and Extrapulmonary TB in Adults and Children

	Initial Phase		Continuation Phase		Comments	
	Drugs	Interval and Duration	Drugs	Interval and Duration		
1	INH RIF PZA EMB ² or SM	Daily for 8 weeks	INH RIF	Daily or 2 or 3 times weekly ³ for 16 weeks ⁴	! EMB or SM should be continued until susceptibility to INH and RIF is shown. ! In areas where less than 4% of cases are resistant to INH (first drug susceptibility test only), EMB or SM may not be necessary for patients with no individual risk factors for drug resistance.	
2	INH RIF PZA EMB ² or SM	Daily for 2 weeks, then	2 times weekly ³ for 6 weeks	INH RIF	2 times weekly ³ for 16 weeks ⁴	! Patients prescribed this regimen should be given directly observed therapy. ! After the initial phase, EMB or SM should be continued until susceptibility to INH and RIF is shown, unless drug resistance is unlikely.
3	INH RIF PZA EMB ² or SM	3 times weekly ³ for 6 months ⁴			! Patients prescribed this regimen should be given directly observed therapy. ! Continue all four drugs for 6 months. ⁵ ! This regimen has been shown to be effective for INH-resistant TB.	

Note. If a patient's drug susceptibility results show resistance to INH, RIF, PZA, EMB, or SM, or if the patient has symptoms, positive smears, or positive cultures after 3 months, consult a TB medical expert.

- ¹ For adults who have smear- and culture-negative pulmonary TB and for adults and children for whom PZA is contraindicated, different regimen options are necessary. Consult a medical expert for further information.
- ² Ethambutol is not recommended for children who are too young to be monitored for changes in their vision. However, ethambutol should be considered for all children who have TB that is resistant to other drugs but susceptible to ethambutol.
- ³ All patients prescribed an intermittent regimen should be given directly observed therapy.
- ⁴ For infants and children with miliary TB, bone and joint TB, or TB meningitis, treatment should last at least 12 months. For adults with these forms of extrapulmonary TB, the patient's response to therapy should be monitored closely. If response is slow or inadequate, treatment may be prolonged on a case-by-case basis.
- ⁵ There is some evidence that SM may be discontinued after 4 months if the isolate is susceptible to all drugs.

INH = isoniazid RIF = rifampin PZA = pyrazinamide SM = streptomycin EMB = ethambutol



Table 4.3
Dosage Recommendations for the Treatment of TB
in Children¹ and Adults

Drug	Dose in mg/kg (maximum dosage in parentheses)					
	Daily		2 times/week ²		3 times/week ²	
	Children	Adults	Children	Adults	Children	Adults
Isoniazid (INH)	10-20 (300 mg)	5 (300 mg)	20-40 (900 mg)	15 (900 mg)	20-40 (900 mg)	15 (900 mg)
Rifampin (RIF)	10-20 (600 mg)	10 (600 mg)	10-20 (600 mg)	10 (600 mg)	10-20 (600 mg)	10 (600 mg)
Pyrazinamide (PZA)³	15-30 (2 gm)	15-30 (2 gm)	50-70 (4 gm)	50-70 (4 gm)	50-70 (3 gm)	50-70 (3 gm)
Ethambutol (EMB)⁴	15-25	15-25	50	50	25-30	25-30
Streptomycin (SM)³	20-40 (1 gm)	15 (1 gm)	25-30 (1.5 gm)	25-30 (1.5 gm)	25-30 (1.5 gm)	25-30 (1.5 gm)

Note. Doses based on weight must be adjusted as the patient's weight changes.

¹ Children younger than 12 years old.

² All patients prescribed an intermittent regimen should be given directly observed therapy.

³ Pyrazinamide and streptomycin should not be used to treat pregnant women.

⁴ Ethambutol is not recommended for children who are too young to be monitored for changes in their vision. However, ethambutol should be considered for all children who have TB that is resistant to other drugs but susceptible to ethambutol.



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HIV-infected people should
be closely monitored for their
response to treatment.
.....

.....
Infants and children with
miliary TB, bone and joint
TB, or TB meningitis should
receive at least 12 months of
treatment.
.....

.....
Treatment for pregnant
women who have TB should
begin as soon as TB is
diagnosed.
.....

.....
The treatment of TB is
essentially the same for
children and adults.
.....

Special Situations

People with HIV infection. The treatment regimens in Table 4.2 are also effective for people with HIV infection. However, HIV-infected people should be closely monitored for their response to treatment. If they do not seem to be responding to treatment, they should be reevaluated.

People with extrapulmonary TB. In general, regimens that are adequate for treating pulmonary TB are also effective for treating extrapulmonary TB. However, infants and children with miliary TB, bone and joint TB, or TB meningitis should receive **at least 12 months** of treatment.

Pregnant women. Treatment should not be delayed for pregnant women who have TB disease; rather, it should begin as soon as TB is diagnosed. The preferred initial regimen for pregnant women who have TB is isoniazid, rifampin, and ethambutol for **at least 9 months**. In most cases, pyrazinamide should NOT be used because there is not enough information about how this drug affects the fetus. Streptomycin should NOT be used because it has been shown to have harmful effects on the fetus.

Children. The treatment of TB is essentially the same for children and adults. However, ethambutol generally is not recommended for children who are too young to be monitored for changes in their vision. (Streptomycin should be used instead.) Also, infants and children with miliary TB, bone and joint TB, or TB meningitis should receive **at least 12 months** of treatment. Infants who are suspected of having TB should be treated immediately because they are likely to develop life-threatening forms of TB very soon after infection.



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The treatment of drug-resistant TB should be done under the supervision of a medical expert who is familiar with the treatment of drug-resistant TB.
.....

.....
When TB is resistant to isoniazid and rifampin, treatment can last 2 years or longer.
.....

Alternative Regimens

People with isoniazid-resistant TB. Isoniazid-resistant TB can be treated with the recommended 6-month, four-drug regimen. It can also be treated with rifampin and ethambutol for **12 months**. The treatment of drug-resistant TB should be done under the supervision of a medical expert who is familiar with the treatment of drug-resistant TB.

People with TB resistant to isoniazid and rifampin (multidrug-resistant TB). It is more difficult to treat multidrug-resistant TB than it is to treat drug-susceptible TB. More drugs are required to treat multidrug-resistant TB, and these drugs are less effective and more likely to cause adverse reactions. When TB is resistant to isoniazid and rifampin, treatment can last **2 years or longer**. As a last resort, some patients with multidrug-resistant TB undergo surgery to remove part of the infected site.



Study Questions 4.17-4.18

4.17. What is directly observed therapy? Why should it be considered for all patients?

4.18. In what special situations should treatment for TB disease last longer than the usual course of treatment?

Answers on page 50.



Case Study 4.3

An 18-month-old girl is admitted to the hospital because of meningitis. Doctors discover that her grandmother had pulmonary TB and was treated with a 6-month regimen. The medical evaluation of the child confirms the diagnosis of TB meningitis.

How long should the child be treated?

Answer on page 54.

.....
Before starting treatment,
adult patients should have
baseline tests to help detect
any abnormalities that may
complicate treatment.
.....

Monitoring for Adverse Reactions

Before starting treatment, adult patients should have certain blood tests and vision tests to help detect any abnormalities that may complicate treatment. For children, only vision tests are necessary unless there are other medical conditions that may complicate treatment. Follow-up tests should be done periodically if the results of the baseline tests indicate abnormalities or if the patient has symptoms that may be due to adverse reactions.



.....
All patients being treated for TB disease should be educated about the symptoms caused by adverse reactions to the drugs they are taking.
.....

As with patients receiving preventive therapy, all patients being treated for TB disease should be **educated about the symptoms that are caused by adverse reactions** to the drugs they are taking (Table 4.4). The patients should be warned about the symptoms of insignificant side effects, such as the orange discoloration of the urine from rifampin, as well as the symptoms of potentially serious side effects, such as vomiting or abdominal pain. Patients should be instructed to seek medical attention immediately if they have symptoms of a serious side effect.

.....
All patients should be seen by a clinician at least monthly during treatment and evaluated for possible adverse reactions.
.....

All patients should be **seen by a clinician at least monthly** during treatment and evaluated for possible adverse reactions. During this evaluation, clinicians should ask patients whether they have any of the symptoms that may be due to adverse reactions and examine patients for signs of possible adverse reactions. Also, public health workers who have regular contact with patients should ask patients about adverse reactions at every visit. If a patient has symptoms of an adverse reaction, the public health worker should

- # Instruct the patient to stop the medication if the symptoms are serious (before working with TB patients, public health workers should be educated about which symptoms are serious)
- # Report the situation to a clinician and arrange for a medical evaluation right away
- # Note the symptoms on the patient's form



Table 4.4
Common Adverse Reactions to TB Drugs

Caused by	Adverse Reaction	Signs and Symptoms
Any drug	Allergic reactions	Skin rash
Ethambutol	Eye damage	Blurred or changed vision Changed color vision
Isoniazid Pyrazinamide Rifampin	Hepatitis	Abdominal pain Abnormal liver function test results Dark urine Fatigue Fever for 3 or more days Flulike symptoms Lack of appetite Nausea Vomiting Yellowish skin or eyes
Isoniazid	Nervous system damage	Dizziness Tingling or numbness around the mouth
	Peripheral neuropathy	Tingling sensation in hands and feet
Pyrazinamide	Stomach upset	Stomach upset, vomiting, lack of appetite
	Increased uric acid	Abnormal uric acid level Joint aches Gout (rare)
Rifampin	Bleeding problems	Easy bruising Slow blood clotting
	Discoloration of body fluids	Orange urine, sweat, or tears Permanently stained soft contact lenses
	Drug interactions	Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment
	Sensitivity to the sun	Frequent sunburn
Streptomycin	Ear damage	Balance problems Hearing loss Ringing in the ears
	Kidney damage	Abnormal kidney function test results



Study Questions 4.19-4.20

4.19. Name the drug or drugs that may cause each of the following symptoms or adverse reactions.

Ear damage:

Hepatitis:

Eye damage:

Orange discoloration of the urine:

4.20. How often should patients be monitored for adverse reactions to TB drugs?

Answers on pages 50-51.



Case Study 4.4

You are assigned to deliver medications to TB patients as part of the directly observed therapy program where you work. When you visit Mr. Jackson's house, you ask him how he is feeling. He tells you that he was up all night vomiting.

What are the possible causes?

Answer on page 54.

Case Study 4.5

Ms. Young, a patient who started treatment for TB disease last week, calls the TB clinic to complain that her urine has changed to a funny color.

Name two possible causes, and explain how each would affect the color of the urine.

Answer on page 55.





Patients who are not receiving directly observed therapy should be monitored carefully for adherence to treatment.

.....

The best way to ensure adherence to treatment is to use directly observed therapy.

.....

Clinicians can evaluate a patient's response to treatment by checking to see whether the patient still has symptoms of TB.

.....

Patients whose symptoms do not improve during the first 2 months of treatment, or whose symptoms worsen after improving initially, should be reevaluated.

.....

Patients who are not receiving directly observed therapy should be monitored carefully for adherence to treatment. This can be done in at least four ways:

- # Check to see whether the patient is reporting to the clinic as scheduled
- # Ask the patient to bring the prescribed medications to each clinic visit and count the number of pills to determine how many have been taken
- # Use special urine tests to detect the presence of the prescribed medication in the urine
- # Assess the patient's clinical response to treatment

None of these methods can be used to prove that a patient is taking every dose of the prescribed medication. **The best way to ensure adherence to treatment is to use directly observed therapy.**

Evaluating Patients' Response to Treatment

Clinicians use three methods to determine whether a patient is responding to treatment. First, they can check to see whether the patient still has symptoms of TB (**clinical evaluation**). Although each patient responds to treatment at a different pace, all patients' TB symptoms should gradually improve and eventually go away. Patients whose symptoms do not improve during the first 2 months of treatment, or whose symptoms worsen after improving initially, should be reevaluated.

Public health workers who have regular contact with patients should pay attention to the patients' improvement. If a patient has symptoms of TB (or of adverse reactions), they should report the situation to the clinician and arrange for a medical evaluation right away. They should also note the symptoms on the patient's forms.



.....
For more than 85% of patients who are treated with isoniazid and rifampin, cultures will convert to negative after the patient has received 2 months of treatment.
.....

Second, clinicians can check a patient's response to treatment by doing a **bacteriologic examination of the sputum or other specimens**. Specimens should be examined at least every month until the culture results have converted from positive to negative. For more than 85% of patients who are treated with isoniazid and rifampin, cultures will convert to negative after the patient has received 2 months of treatment. After conversion is documented, patients should have at least one more smear examination and culture at the end of treatment. Any patient whose culture results have not become negative after 2 months of treatment, or whose culture results become positive after being negative, should be carefully reevaluated.

.....
Patients should have a chest x-ray at the end of treatment so that it can be compared with any chest x-rays given later on.
.....

Third, clinicians can use x-rays to monitor a patient's response to treatment. Repeated x-rays are not as important as monthly bacteriologic and clinical evaluations. However, patients should have an x-ray at the end of treatment. This x-ray can be compared with any x-rays given later on. X-rays are also useful for patients who have negative culture results before treatment or who have certain types of extrapulmonary TB, such as bone and joint TB. In these patients, the bacteriological response may be difficult to assess, and the clinician may have to rely on the clinical and x-ray responses.

.....
The tuberculin skin test cannot be used to determine whether a patient is responding to treatment.
.....

The tuberculin skin test **cannot be used** to determine whether a patient is responding to treatment. This is because most people who have a positive skin test reaction will have a positive reaction if they are skin tested later in their lives, regardless of whether they have received treatment (see Module 3, Diagnosis of Tuberculosis Infection and Disease).



.....
Any patient who has not responded to treatment after 2 months or who has relapsed should be reevaluated promptly.
.....

Reevaluating Patients Who Do Not Respond to Treatment or Who Relapse

Patients should be reevaluated promptly if their

- # Symptoms do not improve during the first 2 months of therapy
- # Symptoms worsen after improving initially
- # Culture results have not become negative after 2 months of treatment
- # Culture results become positive after being negative

Reevaluating the patient means checking for drug resistance by repeating the drug susceptibility tests and assessing whether the patient has been taking medication as prescribed.

The treatment of TB can be complicated, especially in patients who fail to respond to treatment, who relapse, or who have drug-resistant TB or adverse reactions to medications. A new regimen may be required, and treatment may last longer. Clinicians who do not have experience with these situations should consult a medical expert.



Study Questions 4.21-4.25

- 4.21. Name four ways that clinicians can assess whether a patient is adhering to treatment.**
- 4.22. What is the best way to ensure that a patient adheres to treatment?**
- 4.23. How can clinicians determine whether a patient is responding to treatment?**
- 4.24. Under what circumstances should patients be reevaluated?**
- 4.25. What does reevaluating the patient mean?**

Answers on pages 51-52.



Case Study 4.6

Mr. Vigo was diagnosed with smear-positive pulmonary TB in January. He was treated with isoniazid, rifampin, and pyrazinamide by his private physician. He visited his physician again in March. His drug susceptibility test results were not available at the time of this appointment. Nevertheless, the physician discontinued his prescription of pyrazinamide and gave him refills of isoniazid and rifampin. Mr. Vigo visited his physician again in April. He had a persistent cough, and his sputum smear was found to be positive.

What should be done next?

Answer on page 55.



What Is the Role of the Public Health Worker in TB Treatment?

Public health workers in TB programs and other facilities play an important role in helping patients complete preventive therapy or treatment for TB disease. Many public health workers provide directly observed therapy (DOT) or have regular contact with TB patients in clinics, nursing homes, drug treatment centers, or other facilities. At each visit with a patient, public health workers should look for **signs and symptoms of adverse reactions** to the medication. For this reason, public health workers must be familiar with the signs and symptoms of adverse reactions to the drugs commonly used to treat TB. If a patient has symptoms of an adverse reaction, the public health worker should

.....
At each visit with a TB patient, public health workers should look for signs and symptoms of adverse reactions to the medication.
.....

- # Instruct the patient to stop the medication if the symptoms are serious (before working with TB patients, public health workers should be educated about which symptoms are serious)
- # Report the situation to a clinician and arrange for a medical evaluation right away
- # Note the symptoms on the patient's form

.....
Public health workers can help monitor a patient's response to treatment for TB disease by looking for symptoms of TB disease.
.....

Also, public health workers can help monitor a patient's response to treatment for TB disease by looking for **symptoms of TB disease**. Patients receiving treatment for TB disease usually have symptoms at the beginning of therapy, such as coughing, fatigue, and fever. These symptoms should gradually improve and eventually go away. At each visit with a patient, public health workers should pay attention to the patient's improvement. If a patient has symptoms of TB, public health workers should

- # Report the situation to a clinician and arrange for a medical evaluation right away
- # Note the symptoms on the patient's form



In addition to providing DOT, public health workers may be responsible for locating patients who have missed DOT visits or clinic appointments and helping them return to treatment. They may also educate patients and their families about TB, serve as interpreters, arrange and provide transportation for patients, and refer patients to other social services as needed. Finally, in many areas public health workers work with physicians in private practice (physicians who do not work in the health department) to make sure that their TB patients complete an adequate regimen for TB treatment.

Study Question 4.26

4.26. What should a public health worker do if he or she notices that a patient has symptoms of an adverse reaction?

Answer on page 52.



Case Study 4.7

Ms. DeVonne began treatment for pulmonary TB disease 2 months ago, at the beginning of September. You have been giving her directly observed therapy. During the first few weeks of therapy, you noticed that Ms. DeVonne's symptoms were improving a little. However, at a visit in October, you see that Ms. DeVonne is coughing up blood, and she tells you that she feels like she has a fever.

What should you do?

Answer on page 56.



SUMMARY

Preventive therapy is medication that is given to people who have TB infection to prevent them from developing TB disease. High-risk people should be evaluated for preventive therapy if they have a positive skin test reaction, regardless of their age. Others should be evaluated for preventive therapy if they have a positive skin test reaction and they are younger than 35 years old. Sometimes preventive therapy is given to people who have a negative skin test reaction, such as high-risk contacts and children younger than 6 months old who have been exposed to TB.

All patients being considered for preventive therapy should receive a medical evaluation to

- # Exclude the possibility of TB disease
- # Determine whether they have ever been treated for TB infection or disease
- # Identify any medical problems that may complicate therapy or require more careful monitoring

People who are suspected of having TB disease or who have been adequately treated for TB infection or disease should not be given preventive therapy.

The usual regimen for preventive therapy is isoniazid given daily for 6 months. Children should receive 9 months of preventive therapy; HIV-infected persons should receive 12 months. Patients should be evaluated every month for signs of hepatitis and other adverse reactions to isoniazid. They should also be educated about the symptoms caused by adverse reactions to isoniazid and instructed to seek medical attention immediately if these symptoms occur. In addition, people at greatest risk for hepatitis should have liver function tests before starting isoniazid preventive therapy and every month during therapy.

TB disease must be treated for at least 6 months; in some cases, treatment lasts even longer. In most areas of the country, the initial regimen for treating TB disease should include four drugs: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. When the drug susceptibility results are available, clinicians may change the regimen accordingly. TB disease must be treated with at least two drugs to which the bacilli are susceptible. Using only one drug to treat TB disease can create a population of tubercle bacilli that is resistant to



that drug. Drug resistance can also develop when patients do not take treatment as prescribed. Thus, to prevent relapse and drug resistance, clinicians must prescribe an adequate regimen and make sure that patients adhere to treatment. The best way to ensure that patients adhere to treatment is to use directly observed therapy.

There are several options for daily and intermittent treatment. For children with certain types of extrapulmonary TB, pregnant women, and people with drug-resistant TB, treatment may last longer or involve different regimens. Treatment of drug-resistant TB should be done under the supervision of a medical expert who is familiar with the treatment of drug-resistant TB.

All patients being treated for TB disease should be educated about the symptoms caused by adverse reactions to the drugs they are taking and instructed to seek medical attention immediately if they have symptoms of a serious side effect. Patients should be seen by a clinician at least monthly during treatment and evaluated for possible adverse reactions. In addition, before starting treatment, patients should have baseline tests to help clinicians detect any abnormalities that may complicate treatment.

Patients who are not receiving directly observed therapy should be carefully monitored for adherence to treatment. The only way to ensure adherence to treatment is to use directly observed therapy.

To determine whether a patient is responding to treatment, clinicians should do clinical evaluations and bacteriologic evaluations during treatment. Patients should be carefully reevaluated if their

- # Symptoms do not improve during the first 2 months of treatment
- # Symptoms worsen after improving initially
- # Culture results have not become negative after 2 months of treatment
- # Culture results become positive after being negative

In certain situations, clinicians may also use x-rays to monitor a patient's response to treatment.

The treatment of TB can be complicated, especially in patients who fail to respond to treatment, who relapse, or who have drug-resistant TB or adverse reactions to medications. Clinicians who do not have experience with these situations should consult a medical expert.



At each visit with a patient, public health workers should look for signs and symptoms of adverse reactions to the medication. If a patient has symptoms of an adverse reaction, the public health worker should

- # Instruct the patient to stop the medication if the symptoms are serious (before working with TB patients, public health workers should be educated about which symptoms are serious)
- # Report the situation to a clinician and arrange for a medical evaluation right away
- # Note the symptoms on the patient's form

Also, public health workers should pay attention to the patient's improvement. If a patient has symptoms of TB, public health workers should

- # Report the situation to a clinician and arrange for a medical evaluation right away
- # Note the symptoms on the patient's form

Additional Reading

American Lung Association/American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med.* 1994;149:1359-1374.

Centers for Disease Control. Management of persons exposed to multidrug-resistant tuberculosis. *MMWR.* 1992;41(RR-11).

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Core Curriculum on Tuberculosis, 3rd ed. Atlanta: Centers for Disease Control and Prevention; 1994.



ANSWERS TO STUDY QUESTIONS

4.1. What is the purpose of preventive therapy? (page 5)

The purpose of preventive therapy is to prevent people with TB infection from developing TB disease.

4.2. Which groups of people should receive high priority for preventive therapy if they have a positive skin test reaction, regardless of their age? Name six. (page 6)

- # People with HIV infection
- # Close contacts of people with infectious TB disease
- # People whose skin test reaction converted from negative to positive within the past 2 years
- # People with chest x-ray findings suggestive of previous TB disease
- # People who inject illicit drugs
- # People with medical conditions that appear to increase the risk for TB disease

4.3. Which groups of people should receive high priority for preventive therapy if they have a positive skin test reaction and are younger than 35? Name five. (page 6)

- # People born in areas of the world where TB is common (for example, Asia, Africa, or Latin America)
- # Low-income groups with poor access to health care
- # People who live in residential facilities (for example, nursing homes or correctional facilities)
- # Children younger than 4 years old
- # People in other groups as identified by local public health officials



4.4. In what circumstances may preventive therapy be given to people who have a negative tuberculin skin test reaction? (pages 7-8)

Some close contacts may start taking preventive therapy if they have a negative skin test reaction but less than 10 weeks have passed since they were last exposed to TB. These contacts include

- # High-risk contacts who have a negative skin test reaction (including contacts who are anergic). High-risk contacts are young children, adolescents, HIV-infected people, and others who may develop TB very quickly after infection.
- # Close contacts who have a negative skin test reaction, if many other close contacts have a positive skin test reaction

These contacts should be retested 10 weeks after they were last exposed to TB. If they have a negative skin test reaction, they can stop taking preventive therapy. (HIV-infected contacts may be given a full course of preventive therapy, regardless of their skin test results.) If they have a positive skin test reaction, they should continue to take preventive therapy.

Also, children younger than 6 months old who have been exposed to TB should start taking preventive therapy, even if they have a negative skin test reaction. The children should be retested when they are 6 months old. If they have a negative skin test reaction and 10 weeks have passed since they were last exposed to TB, the preventive therapy may be stopped.

4.5. Name three reasons why patients should receive a medical evaluation before starting preventive therapy. (page 10)

All patients being considered for preventive therapy should receive a medical evaluation to

- # Exclude the possibility of TB disease
- # Determine whether they have ever been treated for TB infection or disease
- # Identify any medical problems that may complicate therapy or require more careful monitoring



4.6. Why is it important to exclude the possibility of TB disease before giving a patient preventive therapy? (page 10)

It is important to exclude the possibility of TB disease because treating TB disease with a preventive therapy regimen (usually a single drug) can lead to drug resistance.

4.7. What is the usual preventive therapy regimen? How is it different for children and HIV-infected people? (page 12)

The usual regimen for preventive therapy is isoniazid given daily for 6 months. Children should receive at least 9 months of preventive therapy; HIV-infected persons should receive 12 months of preventive therapy.

4.8. What preventive therapy regimen is recommended for people with a positive skin test reaction who have been exposed to isoniazid-resistant TB? (page 13)

Preventive therapy with rifampin is recommended in this situation.

4.9. What adverse reactions may be caused by isoniazid? Name two, and define each. (pages 15-16)

Isoniazid may cause hepatitis or peripheral neuropathy. Hepatitis is damage to the liver. Peripheral neuropathy is damage to the sensory nerves of the hands and feet.

4.10. What are the symptoms of hepatitis? (page 15)

The common symptoms of hepatitis are nausea, vomiting, abdominal pain, fatigue, and dark urine.

4.11. How often should patients be evaluated for signs and symptoms of adverse reactions during preventive therapy? (page 16)

All persons receiving preventive therapy should be evaluated at least monthly during therapy for signs and symptoms of adverse reactions. During each monthly evaluation, clinicians should ask patients whether they have nausea, abdominal pain, or any of the other symptoms that may be caused by adverse reactions. In addition, they should examine patients for signs of these adverse reactions.



4.12. Who is at greatest risk for hepatitis? What special precautions should be taken for these patients? (page 16)

The people at greatest risk for hepatitis are

- # People 35 years of age and older
- # People with a history of liver disease
- # People who abuse alcohol
- # People who inject illicit drugs
- # People who are taking other medications that may increase the risk of hepatitis

These patients should have liver function tests before starting isoniazid preventive therapy and every month during therapy. In addition, more careful monitoring — and possibly more liver function tests — should be considered for black and Hispanic women because they may be at increased risk for isoniazid-associated hepatitis.

4.13. Why must TB disease be treated for at least 6 months? (page 19)

TB disease must be treated for at least 6 months in order to kill all of the tubercle bacilli. Most of the bacilli are killed during the first 8 weeks of treatment (initial phase). However, a few bacilli become dormant (inactive), and they can remain dormant for a long time. The drugs used to treat TB do not work as well against dormant bacilli as they do against bacilli that are growing (active). Therefore, treatment must be continued for several more months to kill these few remaining bacilli (continuation phase). If treatment is not continued for a long enough time, some bacilli may survive and cause TB disease at a later time (relapse).

4.14. Which four drugs are recommended for the initial treatment of TB disease? (page 19)

In most areas of the country, the initial regimen for treating TB disease should include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and either ethambutol (EMB) or streptomycin (SM). When the drug susceptibility results are available, clinicians may change the regimen accordingly. In areas where less than 4% of cases are resistant to INH (first drug susceptibility test only), three drugs (INH, RIF, and PZA) may be adequate for the initial regimen.



4.15. Why should at least two drugs be used to treat TB disease? (page 21)

Using only one drug to treat TB disease can create a population of tubercle bacilli that is resistant to that drug. When two or more drugs are used together, each drug helps prevent the emergence of bacilli that are resistant to the other drugs.

4.16. Name two factors that can lead to drug resistance. (page 21)

Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment or when patients do not follow treatment regimens as prescribed.

4.17. What is directly observed therapy? Why should it be considered for all patients? (page 23)

Directly observed therapy means that a health care worker or another designated person watches the patient swallow each dose of the prescribed drugs. This method of treatment should be considered for all patients because there is no way to predict reliably which patients will adhere to treatment.

4.18. In what special situations should treatment for TB disease last longer than the usual course of treatment? (pages 27-28)

Infants and children with miliary TB, bone and joint TB, or TB meningitis should receive at least 12 months of treatment.

Pregnant women with TB should receive at least 9 months of treatment.

Treatment for isoniazid-resistant TB can last 12 months when a regimen of rifampin and ethambutol is used, and treatment for multidrug-resistant TB can last 2 years or longer.

4.19. Name the drug or drugs that may cause each of the following symptoms or adverse reactions. (page 32)

Ear damage: streptomycin

Hepatitis: isoniazid, pyrazinamide, rifampin

Eye damage: ethambutol

Orange discoloration of the urine: rifampin



4.20. How often should patients be monitored for adverse reactions to TB drugs?
(page 31)

All patients should be seen by a clinician at least monthly during treatment and evaluated for possible adverse reactions. During this evaluation, clinicians should ask patients whether they have any of the symptoms that may be due to adverse reactions and examine patients for signs of possible adverse reactions. Also, public health workers who have regular contact with patients should ask patients about adverse reactions at every visit.

4.21. Name four ways that clinicians can assess whether a patient is adhering to treatment.
(page 35)

- # Check to see whether the patient is reporting to the clinic as scheduled
- # Ask the patient to bring the prescribed medications to each clinic visit and count the number of pills to determine how many have been taken
- # Use special urine tests to detect the presence of the prescribed medication in the urine
- # Assess the patient's clinical response to therapy

4.22. What is the best way to ensure that a patient adheres to treatment? (page 35)

The best way to ensure adherence to therapy is to use directly observed therapy.

4.23. How can clinicians determine whether a patient is responding to treatment? (pages 35-36)

To determine whether a patient is responding to therapy, clinicians should do clinical evaluations and bacteriologic evaluations during therapy. Clinicians may also use x-rays to monitor a patient's response to treatment, especially in patients who have negative culture results before treatment or who have certain types of extrapulmonary TB.



4.24. Under what circumstances should patients be reevaluated? (page 37)

Patients should be reevaluated promptly if their

- # Symptoms do not improve during the first 2 months of therapy
- # Symptoms worsen after improving initially
- # Culture results have not become negative after 2 months of treatment
- # Culture results become positive after being negative

4.25. What does reevaluating the patient mean? (page 37)

Reevaluating the patient means checking for drug resistance by repeating the drug susceptibility tests and assessing whether the patient has been taking medication as prescribed.

4.26. What should a public health worker do if he or she notices that a patient has symptoms of an adverse reaction? (page 40)

The public health worker should

- # Instruct the patient to stop the medication if the symptoms are serious (before working with TB patients, public health workers should be educated about which symptoms are serious)
- # Report the situation to a clinician and arrange for a medical evaluation right away
- # Note the symptoms on the patient's form



ANSWERS TO CASE STUDIES

4.1. You are sent to visit the home of a TB patient who was admitted to the hospital last week and diagnosed with infectious TB disease. Living in the home are his wife and his 1-year-old daughter. Neither one has symptoms of TB disease. You give them both a tuberculin skin test and return 2 days later to read the results. You find that the wife has 14 mm of induration, but the daughter has no induration.

Should either one start preventive therapy?

Yes, both should start preventive therapy.

Why or why not?

The wife is a close contact of someone with infectious TB disease, and she has a positive skin test reaction (≥ 5 mm for close contacts). Therefore, after receiving a medical evaluation (to rule out TB disease, determine whether she has ever been treated for TB infection or disease, and identify any medical problems that may complicate therapy), she should complete an entire course of preventive therapy, regardless of her age.

The daughter is also a close contact. Currently, she has a negative skin test reaction. However, only 1 week has passed since she last spent time with her infectious father. It is possible that not enough time has passed for her to be able to react to the tuberculin skin test. In other words, her reaction may be a false-negative reaction. At this point, it is impossible to determine whether she has TB infection. In addition, because she is a young child, she may develop TB very quickly after infection.

For these reasons, the daughter should start preventive therapy now and be retested 10 weeks after she last spent time with her father. If she has a negative reaction to the repeat skin test, she may stop taking preventive therapy. If she has a positive reaction, she should complete an entire course of preventive therapy (9 months for children).



- 4.2. A 65-year-old man is prescribed isoniazid preventive therapy because he is a close contact of a person with infectious TB and he has an induration of 20 mm to the tuberculin skin test. His baseline liver function tests are normal, but he drinks a six-pack of beer every day.**

What kind of monitoring is necessary for this patient while he is taking isoniazid?

Even though his liver function tests are normal, this man is at high risk of isoniazid-associated hepatitis because he is older than 35 and abuses alcohol. He should be educated about the symptoms of adverse reactions to isoniazid and be instructed to seek medical attention immediately if these symptoms occur. Furthermore, once a month, he should be seen by a clinician. The clinician should ask him about his symptoms, examine him for signs of adverse reactions, and perform liver function tests once a month.

- 4.3. An 18-month-old girl is admitted to the hospital because of meningitis. Doctors discover that her grandmother had pulmonary TB and was treated with a 6-month regimen. The medical evaluation of the child confirms the diagnosis of TB meningitis.**

How long should the child be treated?

Infants and children with miliary TB, bone and joint TB, or TB meningitis should be treated for at least 12 months.

- 4.4. You are assigned to deliver medications to TB patients as part of the directly observed therapy program where you work. When you visit Mr. Jackson's house, you ask him how he is feeling. He tells you that he was up all night vomiting.**

What are the possible causes?

His vomiting may be a symptom of hepatitis (caused by isoniazid, rifampin, and pyrazinamide) or of stomach upset due to pyrazinamide. This situation should be reported to the clinician, and Mr. Jackson should be given a medical evaluation right away.



4.5. Ms. Young, a patient who started treatment for TB disease last week, calls the TB clinic to complain that her urine has changed to a funny color.

Name two possible causes, and explain how each would affect the color of the urine.

One possible cause is the discoloration of body fluids, a common side effect of rifampin. This would cause Ms. Young's urine to turn orange. The clinic nurse, physician, or public health worker should explain to Ms. Young that orange urine and other body fluids is a side effect of rifampin and that this is NOT a serious condition.

Another possible cause is hepatitis, which can be caused by isoniazid, rifampin, or pyrazinamide. Hepatitis, a serious condition, would cause Ms. Young's urine to turn dark. If Ms. Young's urine is dark, the situation should be reported to the clinician and Ms. Young should receive a medical examination right away.

4.6. Mr. Vigo was diagnosed with smear-positive pulmonary TB in January. He was treated with isoniazid, rifampin, and pyrazinamide by his private physician. He visited his physician again in March. His drug susceptibility test results were not available at the time of this appointment. Nevertheless, the physician discontinued his prescription of pyrazinamide and gave him refills of isoniazid and rifampin. Mr. Vigo visited his physician again in April. He had a persistent cough, and his sputum smear was found to be positive.

What should be done next?

Mr. Vigo's persistent cough and positive sputum smear indicate that he is not responding to therapy. The most likely explanations are

- Q That he is not taking his medications as prescribed,
- Q That he has drug-resistant TB and the regimen he has been prescribed is not adequate to treat his TB, or
- Q A combination of the two factors listed above.

The initial drug susceptibility test results should be located, and susceptibility tests should be repeated on a recent sputum specimen. In addition, his adherence should be evaluated, and he should be given directly observed therapy if possible.



- 4.7. Ms. DeVonne began treatment for pulmonary TB disease 2 months ago, at the beginning of September. You have been giving her directly observed therapy. During the first few weeks of therapy, you noticed that Ms. DeVonne's symptoms were improving a little. However, at a visit in October, you see that Ms. DeVonne is coughing up blood, and she tells you that she feels like she has a fever.**

What should you do?

Coughing up blood and feeling feverish are symptoms of TB disease. You should report Ms. DeVonne's symptoms to the clinician and arrange for her to receive a medical evaluation right away. Also, you should note Ms. DeVonne's symptoms on her form.

The fact that Ms. DeVonne's TB symptoms got worse after improving initially indicates that she is not responding to therapy. Because she is receiving directly observed therapy, Ms. DeVonne is probably taking her medications as prescribed. Therefore, the most likely explanation is that she has drug-resistant TB and the prescribed regimen is not adequate to treat the TB.

Ms. DeVonne's initial drug susceptibility test results should be located, and drug susceptibility tests should be repeated on a recent sputum specimen.